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Clinical performance comparison of two medium cut-off dialyzers

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Abstract

Introduction: Medium-cut-off (MCO) dialyzers may beneficially impact outcomes in patients on hemodialysis.

Methods: In a randomized, controlled trial in maintenance hemodialysis patients, the new Nipro ELISIO-17HX MCO dialyzer was compared to the Baxter Theranova 400 filter regarding middle molecule removal. Furthermore, the suitability of two assays for free lambda-light chain (λFLC) detection (Freelite vs. N-Latex) was verified.

Results: ELISIO-HX achieved slightly lower reduction ratios for β_2-microglobulin (71.8 ± 6.0 vs. 75.3 ± 5.8%; $p = 0.001$), myoglobin (54.7 ± 8.6 vs. 64.9 ± 8.7%; $p < 0.001$), and kappa-FLC (62.1 ± 8.8 vs. 56.3 ± 7.7%; $p = 0.021$). λFLC reduction ratios were more conclusive with the Freelite assay and not different between ELISIO-HX and Theranova (28.4 ± 3.9 vs. 38.7 ± 13.4%; $p = 0.069$). The albumin loss of Theranova was considerably higher (2.14 ± 0.45 vs. 0.77 ± 0.25 g; $p = 0.001$) and the Global Removal Score$_{\text{Loss alb}}$ largely inferior (30.6 ± 7.4 vs. 82.4 ± 29.2%/g; $p = 0.006$) to ELISIO-HX.

Conclusions: The new ELISIO-HX expands the choice of dialyzers for MCO hemodialysis.

KEYWORDS

dialysis adequacy, end-stage kidney disease, free light chains, hemodialysis, medium cut-off dialyzer

1 | INTRODUCTION

The range of uremic toxins eliminated by current high-flux dialysis strategies is restricted and covers only solutes not larger than smaller-sized middle molecules [1]. The retention of larger middle molecules of up to 60 kDa is regarded as one factor involved in excess mortality of patients on maintenance hemodialysis therapy [2]. Consequently, in 2017, a first medium cut-off (MCO) dialyzer with a novel permeability-enhanced dialysis membrane was introduced [3]. Meanwhile, several studies have confirmed that the MCO filters (Baxter Theranova series), which are strictly to be used in hemodialysis mode, remove an expanded range of middle molecules more effectively than high-flux dialysis [3–7]. The landmark introductory studies on these novel dialyzers demonstrated a possibly better efficacy for large middle molecule removal even compared to high-volume postdilution hemodiafiltration without leading to excessive albumin loss [3].

Uremic toxins in a molecular range of 15–50 kDa accumulating in renal failure have been associated with inflammation, tissue calcification, and cardiovascular morbidity and mortality in patients with end-stage kidney disease [2]. Compared to low- and high-flux dialysis, recent clinical trials suggest that maintenance hemodialysis with MCO dialyzers may have beneficial effects on certain clinical endpoints [8]. A registry-based Japanese cohort study indicates that hemodialysis with super high-flux dialyzers, which share permeability characteristics of MCO dialyzers, was even associated with a strongly reduced hazard ratio for all-cause mortality [9]. Although a direct correlation of clinical outcomes with the enhanced elimination of larger middle molecules is completely unproven, switching dialyzers in hemodialysis mode is easily performed without problems. Therefore, the trend to MCO dialysis membranes to meet the need of thousands of dialysis patients worldwide for filters with potentially beneficial effects is obvious.

The main purpose of the present study was to compare the clinical performance of two MCO dialyzers, the new Nipro ELISIO-17HX and the reference Theranova 400 dialyzer. In vitro experiments have demonstrated that for this intent the removal of free lambda-light chains (λFLC) may be ideally suited to differentiate between MCO dialysis membranes [10]. In high-flux hemodialysis, λFLC are virtually not removed because they occur in plasma in dimeric form resulting in a molecular weight of 45 kDa [11, 12], which is beyond the high-flux membranes' cut-off. Different assays for automated measurement of λFLC are available, but have led to conflicting results in previous trials [13–15]. Therefore, whether the polyclonal Freelite and the monoclonal N-Latex assay are equally suitable to detect λFLC as a relevant biomarker for clinical characterization of dialysis membranes in end-stage kidney disease was also investigated.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was performed in adherence to the Declaration of Helsinki. Six maintenance dialysis patients on a thrice weekly dialysis regimen were enrolled in a prospective, controlled, cross-over, open-label, and single-center trial. The patients were randomly assigned by lot to receive one hemodialysis treatment with each of two different MCO study dialyzers during a routinely scheduled mid-week session. The two dialyzers were the new Nipro ELISIO-17HX (γ-sterile; K_{UF} 67 ml/h/mm Hg; inner diameter 200 μm, wall thickness 40 μm; polyethersulfone/polyvinylpyrrolidone blend; Nipro Corp., Osaka, Japan) and the reference filter Baxter Theranova 400 (steam-sterile; K_{UF} 48 ml/h/mm Hg; inner diameter 180 μm, wall thickness 35 μm; polyarylethersulfone/polyvinylpyrrolidone blend; Baxter Deutschland GmbH, Germany), both featuring surface areas of 1.7 m^2. To avoid carry-over effects, the two sessions with the study dialyzers were separated by 2 weeks of five consecutive hemodialysis treatments with a standard polyethersulfone high-flux dialyzer (surface area 1.5 m^2; Nipro ELISIO-15H). Ultrapure bicarbonate dialysate was exclusively applied. During the study treatments, blood and dialysate flow rates were set at 300 and 500 ml/min, respectively. Intended treatment duration was 240 min. The target ultrafiltration volumes were set according to individual requirements to achieve the patients' dry weight. Anticoagulation with standard ($n = 5$) or fractionated ($n = 1$) heparin was unchanged adopted from the patients' routinely used regimen.

2.2 | Determination of treatment effects

Plasma concentrations of the small solutes urea, creatinine, and phosphate and the larger solutes β_2-microglobulin (b2M; 11.8 kDa), myoglobin (myo; 17.6 kDa), free kappa light chains (κFLC; 22.5 kDa), α_1-microglobulin (a1M; 33 kDa), and λFLC (45 kDa) were measured to allow calculation of reduction ratios and instantaneous clearances. Furthermore, reduction ratios of the inflammatory proteins interleukin-6 (IL6; 21 kDa) and tumor necrosis factor alpha (TNFa; 17.3 kDa) as well as of albumin (alb; 67 kDa) were determined based on their plasma concentrations. Reduction ratios were calculated after correction of the arterial blood value at the end of dialysis for extracellular volume changes based on differences in the patient's pre- and post-treatment body weight [16]. Calculation of the respective efficacy parameters has been previously described [16]. Additionally, after adaption for the spectrum of proteins determined in the present trial, Global Removal Scores were assessed, according to those recently proposed by Maduell et al. [17]. The following two equations were applied,

$$\text{Global Removal Score}_{\text{RRalb}} = \left(\text{RR}_{\text{urea}} + \text{RR}_{\text{b2M}} + \text{RR}_{\text{myo}} + \text{RR}_{\kappa\text{FLC}} + \text{RR}_{\lambda\text{FLC}}\right)/5 - \text{RR}_{\text{alb}}\,[\%], \quad (1)$$

$$\text{Global Removal Score}_{\text{Loss alb}} = \left(\text{RR}_{\text{urea}} + \text{RR}_{\text{b2M}} + \text{RR}_{\text{myo}} + \text{RR}_{\kappa\text{FLC}} + \text{RR}_{\lambda\text{FLC}}\right) /5/\text{Dialysate loss}_{\text{albumin}}\,[\%/\text{g}], \quad (2)$$

where RR is the reduction ratio of the respective protein in plasma.

Blood samples were drawn from the arterial needle before the treatment and, at 30 and 240 min, from the arterial and venous blood line exclusively during the study and control treatments. An additional arterial blood sample was drawn

at the end of dialysis after reducing the blood flow rate to 50 ml/min and the dialysate flow turned off for 30 s to allow calculation of the single-pool Kt/V using the second generation logarithmic estimate by Daugirdas [18]. Continuous sampling of spent dialysate for mass transfer measurements was carried out as previously described by setting up of a rotating collection pump (Ismatec SA, Glattbrugg-Zurich, Switzerland) at a flow rate of 10 ml/min into the dialysate discharge line via a T-connector throughout the whole treatment duration [3]. A sample was drawn after stirring and concentrations of albumin, b2M, myo, κFLC, a1M, and λFLC were determined. Blood and dialysate samples were processed immediately after collection or stored at −80°C until analysis.

2.3 | Analytical methods

Urea, creatinine, and phosphate were measured with a Cobas c111 clinical analyzer (Roche Diagnostics GmbH, Mannheim, Germany). For the larger proteins albumin, b2M, myo, κFLC, a1M, and λFLC, laser nephelometry (BN ProSpec, Siemens, Eschborn, Germany) was applied on plasma and native dialysate samples after thawing. In addition to the nephelometric N-Latex monoclonal antibody test, λFLC were opposed to the measurement with the Freelite assay (The Binding Site Group Ltd, Birmingham, UK), which uses polyclonal antibodies. TNFa and IL6 were quantified by ELISA (Bio-Techne GmbH, Wiesbaden, Germany). All tests were performed according to the manufacturers' instructions. Hematocrits were measured with an ABX Pentra 60 cell counter (Axon Lab AG, Reichenbach, Germany).

2.4 | Statistical analysis

Descriptive data analysis was performed by calculating mean values ± SDs. Within-subject between-treatment differences and within-subject within-treatment differences were analyzed by a paired *t*-test for normally distributed samples. The Friedman and the Spearman tests were used if normal distribution did not apply. A p value of <0.05 was considered statistically significant. For statistical analyses, the "Minitab 17 Statistical Software" package (Minitab, Inc., State College, PA) was used.

3 | RESULTS

3.1 | Patient characteristics

Six patients (58.2 ± 16.5 years; 4 males, 2 females; 74.1 ± 14.5 kg) were enrolled and completed the trial without experiencing any study-related adverse events including clotting of the extracorporeal circuit or hypotension. All patients had patent arterio-venous fistulae and were on a high-flux dialyzer for more than 1 year prior to the trial. Underlying renal diseases were glomerulonephritis ($n = 3$), diabetic nephropathy ($n = 1$), hypertensive nephropathy ($n = 1$), and renal ischemia from ruptured aortic aneurysm ($n = 1$). The dialysis vintage was 119.5 ± 56.1 months. None of the patients had residual renal function.

Treatment times with each dialyzer were identical and lasted 240 ± 0 min. Blood and dialysate flow rates complied with the study protocol, being 300 ± 0 and 500 ± 0 ml/min, respectively, throughout all treatments. Ultrafiltration volumes were similar ($p = 0.81$) with 2600 ± 562 ml for ELISIO and 2650 ± 740 ml for Theranova.

3.2 | Treatment effects

Indicating adequate small solute removal, the dialysis doses Kt/V achieved with ELISIO and Theranova were 1.65 ± 0.31 and 1.62 ± 0.32 ($p = 0.23$), respectively. Accordingly, instantaneous small solute clearances at 30 and 240 min did not show any differences between the filters (refer to Table 1).

Differences in performance were observed for the larger solutes. Compared to ELISIO, instantaneous clearances (at 30 min, 69 ± 7 vs. 79 ± 7 ml/min, $p = 0.020$; at 240 min, 64 ± 6 vs. 71 ± 4 ml/min; $p = 0.004$) and mass of b2M removed into dialysate (169 ± 90 vs. 189 ± 92 mg; $p = 0.003$) were higher with Theranova (refer to Table 1). This corresponded to an equally higher b2M reduction ratio (75.3 ± 5.8 vs. 71.8 ± 6.0%; $p = 0.001$) (refer to Figure 1). Theranova achieved also higher reduction ratios for myoglobin (64.9 ± 8.7 vs. 54.7 ± 8.6%; $p < 0.001$) and κFLC (62.1 ± 8.8 vs. 56.3 ± 7.7%; $p = 0.021$) than ELISIO. Furthermore, for κFLC, also the mass in dialysate was higher with Theranova (391 ± 131 vs. 300 ± 102 mg; $p = 0.015$). However, the differences in larger solute removal were attributed to an almost three times higher albumin loss with Theranova compared to ELISIO (2136 ± 451 vs. 765 ± 251 mg; $p = 0.001$) (refer to Table 1). In consequence, the loss of albumin was associated with a superior Global Removal Score$_{\text{Loss alb}}$ of 82.4 ± 29.2%/g for ELISIO compared to 30.6 ± 7.4%/g for Theranova ($p = 0.006$), while there was no difference ($p = 0.26$) in the Global Removal Score$_{\text{RRalb}}$ based on the change of albumin concentrations in plasma (refer to Figure 2).

No differences were also observed for the elimination of the inflammatory proteins. Reduction ratios for IL6 (Theranova, 29.5 ± 26.1% vs. ELISIO, 9.0 ± 43.3%;

TABLE 1 Instantaneous plasma clearances and mass removed into dialysate of the different plasma solutes determined

	MW (Da)		Plasma clearance		Mass in dialysate (mg)
			30 min (mL/min)	240 min (mL/min)	
Urea	60	ELISIO	232 ± 4	225 ± 6	-
		Theranova	233 ± 5	227 ± 6	-
Creatinine	113	ELISIO	185 ± 8	171 ± 15	-
		Theranova	187 ± 9	174 ± 12	-
Phosphate	96	ELISIO	192 ± 2	183 ± 7	-
		Theranova	196 ± 4	188 ± 5	-
b2M	11 800	ELISIO	69 ± 7	64 ± 6	169 ± 90
		Theranova	79 ± 7[a]	71 ± 4[b]	189 ± 92[c]
Myoglobin	17 600	ELISIO	52 ± 6	32 ± 8	1.18 ± 0.30
		Theranova	52 ± 8	34 ± 9	1.41 ± 0.55
κFLC	22 500	ELISIO	38 ± 6	26 ± 3	300 ± 102
		Theranova	36 ± 7	28 ± 2	391 ± 131[d]
a1M	33 000	ELISIO	−4 ± 7	−1 ± 12	b.l.d.
		Theranova	7 ± 6	0 ± 6	b.l.d.
λFLC monoclonal	45 000	ELISIO	53 ± 6	49 ± 6	239 ± 87
		Theranova	59 ± 11	49 ± 9	327 ± 92[e]
λFLC polyclonal	45 000	ELISIO	3 ± 6	−3 ± 8	b.l.d.
		Theranova	7 ± 9	6 ± 4	b.l.d.
Albumin	67 000	ELISIO	-	-	765 ± 251
		Theranova	-	-	2136 ± 451[e]

Note: Mean values ± SDs are given. Unless otherwise indicated, no significant differences were observed. Theranova vs. ELISIO.
Abbreviations: a1M, alpha-1-microglobulin; b.l.d., below limit of detection; b2M, beta-2-microglobulin; κFLC, kappa free light chains; λFLC, lambda free light chains; MW, molecular weight.
[a] $p = 0.020$.
[b] $p = 0.004$.
[c] $p = 0.003$.
[d] $p = 0.015$.
[e] $p = 0.001$.

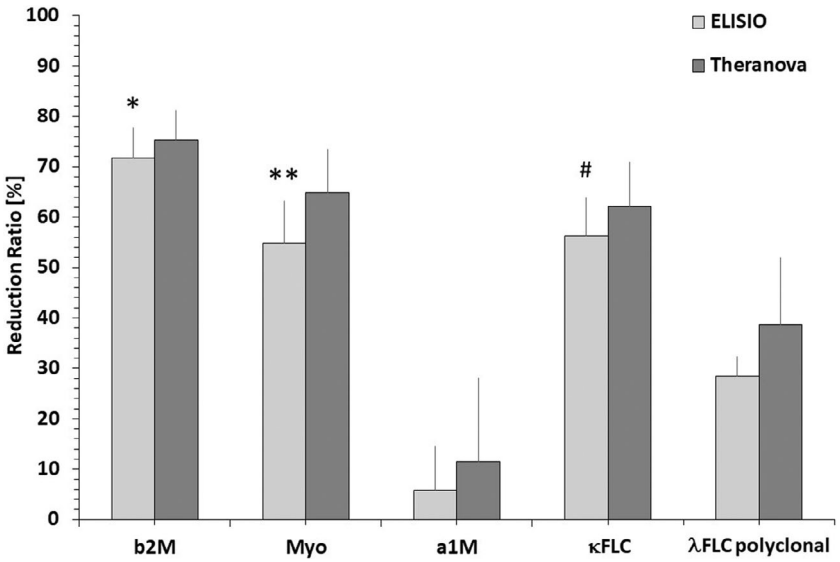

FIGURE 1 Mean plasma reduction ratios ± SDs of the larger proteins. In addition to κFLC ($^{\#}p = 0.021$), slightly higher values were achieved with Theranova for b2M ($^{*}p = 0.001$) and myo ($^{**}p < 0.001$) vs. ELISIO

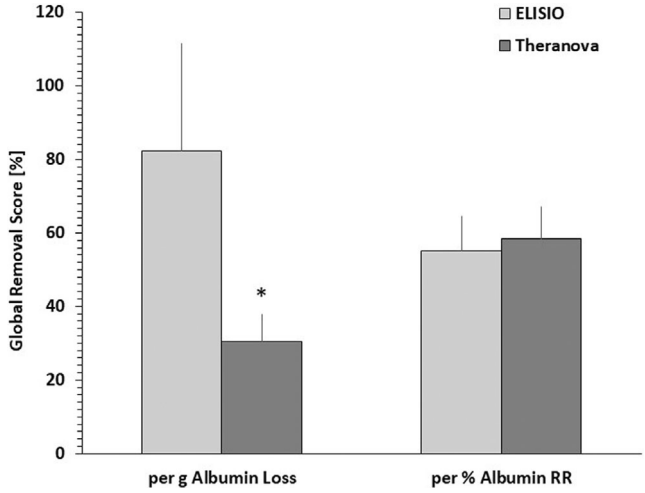

FIGURE 2 Global removal scores based on the combined reduction ratios of the different proteins. Relative to the mass of albumin loss into dialysate, the score achieved with ELISIO was much higher compared to Theranova (*$p = 0.006$), while there was no difference when it was based on the reduction ratio of albumin in plasma. Mean values ± SDs are given

$p = 0.26$) and TNFa (49.3 ± 10.9% vs. 39.1 ± 18.4%; $p = 0.09$) varied considerably.

3.3 | Comparison of mono- and polyclonal λFLC assays

Although, the measurement of the λFLC concentrations with the mono- and polyclonal assays exhibited a good correlation ($r = 0.665$; $p < 0.001$) (refer to Figure 3), the resulting reduction ratios for this protein, which occurs in plasma in form of a dimer [11], differed considerably. By using the monoclonal λFLC assay, the plasma concentrations for ELISIO before and after dialysis were 135.5 ± 57.4 and 47.7 ± 14.4 mg/L and for Theranova 130.2 ± 41.5 and 42.5 ± 8.5 mg/L (refer to Table 2). The reduction ratios even slightly exceeded those achieved for the smaller monomeric κFLC in hemodialysis with both ELISIO and Theranova (62.7 ± 8.8 and 65.4 ± 9.5%, respectively; $p = 0.009$). The reduction ratios determined with the polyclonal λFLC assay contrasted considerably by

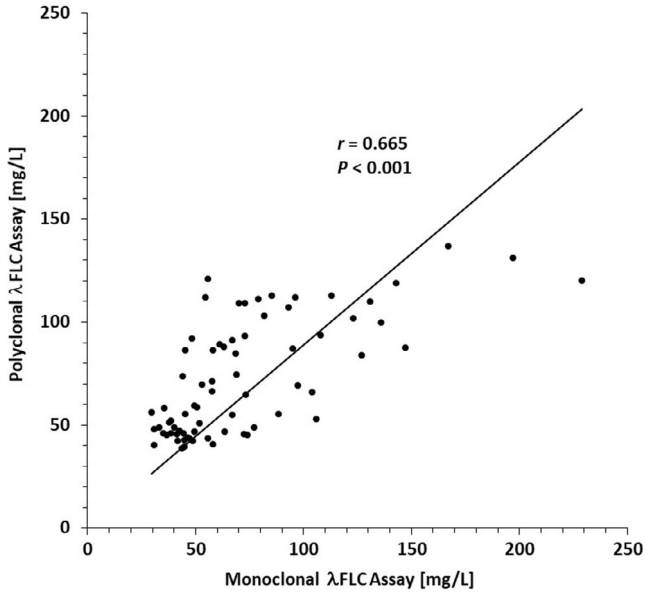

FIGURE 3 Pre- and post-dialysis plasma concentrations of monoclonal and polyclonal λFLC highly correlated ($r = 0.665$; $p < 0.001$)

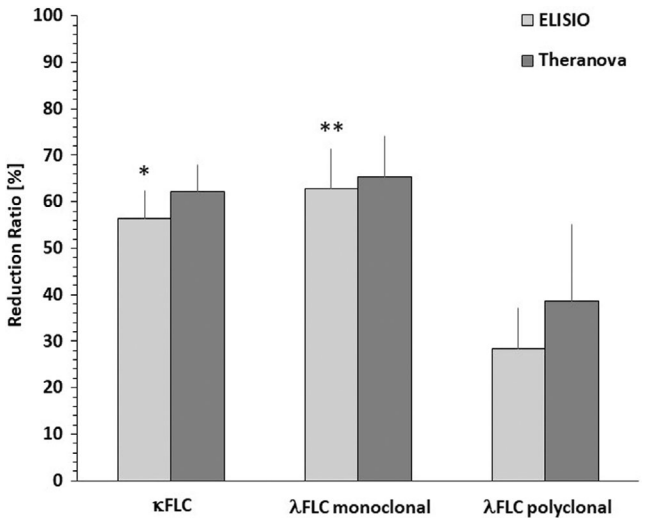

FIGURE 4 Plasma reduction ratios of κFLC as well as of monoclonal and polyclonal λFLC. Differences between ELISIO and Theranova were found for κFLC (*$p = 0.021$) and monoclonal λFLC (**$p = 0.009$). Mean values ± SDs are displayed

		Before (mg/L)	After (mg/L)	Before vs. after p
κFLC	ELISIO	113.8 ± 30.7	48.7 ± 11.8	0.001
	Theranova	120.8 ± 36.5	44.5 ± 12.5	0.001
λFLC monoclonal	ELISIO	135.5 ± 57.4	47.7 ± 14.4	0.006
	Theranova	130.2 ± 41.5	42.5 ± 8.5	0.014
λFLC polyclonal	ELISIO	85.8 ± 36.0	61.5 ± 26.7	0.002
	Theranova	88.7 ± 34.6	52.4 ± 19.1	0.006

Note: Mean values ± SDs are given. Unless otherwise indicated, no significant differences were observed.

TABLE 2 Plasma concentrations of κFLC and λFLC measured with both assays before and after hemodialysis

showing far lower results with both dialyzers (ELISIO, 28.4 ± 3.9%, and Theranova, 38.7 ± 13.4%; $p = 0.069$) (refer to Figure 4), while plasma concentration were also inferior being 85.8 ± 36.0 and 61.5 ± 26.7 mg/L for ELISIO and 88.7 ± 34.6 and 52.4 ± 19.1 mg/L for Theranova before and after dialysis, respectively (refer to Table 2). Independently of the assay applied, no differences between ELISIO and Theranova were observed for λFLC elimination (refer to Table 1 and Figure 4).

4 | DISCUSSION

The results of the present randomized, clinical pilot trial clearly demonstrate that both MCO dialyzers, the Theranova as well as the new ELISIO, eliminate an extended range of middle molecules in hemodialysis including those larger solutes not sufficiently removed by high-flux filters even in hemodiafiltration mode [3]. The efficacy of middle molecule removal achieved with Theranova was essentially consistent with data reported in a recent trial, in which identical settings were applied when performing the dialysis treatments [3]. It was also on a similar level with studies, in which treatment parameters were either different or not as well controlled [4–7]. The mass of albumin loss into dialysate by Theranova (2.1 ± 0.45 g) was to some extent below the previous values observed for this filter by other investigators (about 3 g) [3–5]. With the ELISIO filter, smaller middle molecules were slightly less efficiently cleared compared to Theranova, but this difference could be attributed to much lower albumin loss (0.77 ± 0.25 g), which resulted in a much more favorable Global Removal $Score_{Loss\ alb}$ (ELISIO, 82.4 ± 29.2%/g vs. Theranova, 30.6 ± 7.4%/g) [17].

Uremic toxins in a molecular range of 15–50 kDa accumulating in renal failure, such as cytokines, adipokines, immune-related proteins, growth factors and hormones, have been associated with inflammation, tissue calcification, and cardiovascular morbidity and mortality in patients with end-stage kidney disease [2]. Although the data base is still very scarce, a recent meta-analysis of clinical trials indicates that maintenance MCO hemodialysis may favorably impact on infection events, length of hospital stay, quality of life, recovery after dialysis, pruritus, restless legs syndrome, erythropoiesis resistance index, and iron utilization [8]. A nationwide prospective cohort study analyzing the data of 242 467 maintenance dialysis patients of the Japanese Society for Dialysis Therapy Renal Data Registry investigated the effect of the dialyzer type on 3-year all-cause mortality. With increasing permeability, the hazard ratio for mortality decreased showing most favorable results for super high-flux, that is, type IV and particularly type V dialyzers according to the Japanese classification (b2M clearance 50 to 70 and ≥70 ml/min, respectively, at an albumin loss usually <3 g per session) [9]. A direct correlation of clinical outcomes with the enhanced elimination of larger middle molecules is completely unproven. However, in contrast to online hemodiafiltration which, depending on high-flux dialyzer and settings applied, is also able to remove λFLC significantly at low albumin loss [3, 19, 20], hemodialysis is technically easy to perform, and dialyzers can be switched without problems. Therefore, the trend to MCO dialysis membranes to meet the need of thousands of dialysis patients worldwide for filters with potentially beneficial effects is obvious. Whether the observed small differences in efficacy between the two dialyzers examined translate into any further clinical benefit or, with respect to the differences in albumin retention, even have a negative consequence is currently completely open, albeit unlikely. In any case, a consequential next step would be to compare the effects of the filters on the plasma levels of large middle molecules over a mid-term period. To note, compared to high-flux hemodialysis, the use of the Theranova dialyzer over 3 months reduced these plasma levels in a previous study [6].

Concerning the elimination of λFLC tested with the polyclonal assay and a1M, both representing large middle molecules, no significant differences between ELISIO and Theranova were determined. a1M as a monomer has a molecular weight of 33 kDa [21]. Although its size should actually allow a considerable decrease of the plasma concentrations during MCO dialysis, its instantaneous clearances were negligible and associated with very modest reduction ratios of only about 10% with each dialyzer. The very limited removal is explained by protein-binding forming large high-molecular-mass a1M-protein complexes, which do not allow the passage of bound a1M through MCO dialysis membranes. In human plasma, more than 50% of a1M is bound to immunoglobulin A forming a complex of 190 kDa [22]. Another 7% bind 1:1 and 1:2 to albumin (100–135 kDa) and 1–2% 1:1 and 1:2 to prothrombin (110–145 kDa) [22]. Additional a1M exists as dimers of 60 kDa [21], which is close to the molecular weight of albumin (67 kDa) and, hence, may be removed to a very limited extent.

Like other uremic toxins, λFLC (and κFLC) determined with the Freelite polyclonal antibody assay accumulate progressively with declining renal function, reaching highest serum concentrations in end-stage kidney disease [23]. Polyclonal FLC levels can be regarded as interesting biomarkers because they are associated with patient outcome, independently predicting mortality and further decline of renal function in chronic kidney disease patients [24–27]. Using the Freelite assay to measure FLC, Hutchison et al. were the first to demonstrate a

significant increase of the κ/λ-FLC ratio in patients with chronic kidney disease compared to healthy controls. They proposed a modified κ/λ reference range of 0.37–3.1 to prevent a significant number of these patients being misclassified as having a κ monoclonal gammopathy [23]. Subsequent studies confirmed this finding, but when the polyclonal Freelite test was compared with the monoclonal N-Latex FLC assay, significantly different κ/λ-ratios for the two tests were observed [13, 14]. This observation was also confirmed in a recent study on myeloma patients without renal failure [15]. In contrast to the Freelite assay, the κ/λ-ratio with the N-Latex assay in advanced renal failure was lower and within the range of healthy controls (0.31–1.56) [13, 14]. The discrepancy in κ/λ-ratio of the assays are mainly a consequence of different λFLC results, which are measured considerably higher by the N-Latex test, thereby confirming the results of the present study (plasma concentrations before dialysis, monoclonal λFLC, 132.8 ± 47.8 vs., polyclonal λFLC, 87.3 ± 33.7 mg/L). This observation clearly suggests that the two λFLC assays cannot be used interchangeably in renal failure [14, 28]. The reasons for the difference in assay performance remain completely unclear. Methodologically, the Freelite assay uses polyclonal antibodies, while the N-Latex assay is based on monoclonal antibodies, which may lead to a different reactivity to monomeric compared with dimeric forms of FLC in the uremic milieu [29, 30]. The reactivity may be influenced by a so far unknown interfering low-molecular weight substance erroneously responding to the N-Latex assay, which is cleared during hemodialysis, as hypothesized by Berlanga et al. [31]. Others assumed that the discrepancies observed between the two methods could be attributed to a possible polymerization of FLC [32], which may alter the presentation and detectability of epitopes. If such a FLC polymerization is affected by hemodialysis-induced plasma milieu modifications remains also highly speculative.

Given the existing experiences with the two λFLC assays so far, it was not surprising that the differences in performance had a strong effect on the results of the present clinical characterization of MCO dialysis membranes. Although, a good correlation between the λFLC plasma concentration with the Freelite and the N-Latex test was observed, the reduction ratios differed considerably. For monoclonal λFLC measured with N-Latex, they were 62.7 ± 8.8% with ELISIO and 65.4 ± 9.5% with Theranova, which even slightly exceeded the values determined for κFLC. These values clearly overestimated true λFLC removal. Monomeric FLC in plasma consist mainly of κFLC, which has a chromatographically determined Stokes' radius of 2.3 nm [11]. With a molecular weight of 22.5 kDa and based on the in vitro size excluding characteristics of the Theranova dialysis membrane [10], κFLC reduction ratios somewhat lower than for b2M appear to be conclusive. In contrast, λFLC represent the covalently and non-covalently bound 45 kDa dimer of FLC in plasma with a larger Stokes' radius of 2.8 nm [11]. With respect to the significantly larger albumin (radius of 3.5 nm [11]), which was almost not eliminated as indicated by a reduction ratio of zero and a very limited loss into dialysate, a correct reduction ratio for λFLC has to be expected in the range between κFLC and albumin. Using the Freelite test, the reduction ratios for polyclonal λFLC fulfilled these expectation, being 28.4 ± 3.9% with ELISIO and 38.7 ± 13.4% with Theranova. The finding for Theranova essentially confirms those from previous studies, in which similar (39%) [7] or slightly higher reduction ratios of 43 and 44% were determined for polyclonal λFLC and also for κFLC (63 and 70% vs. 62% in the present trial) [4, 6]. The small differences may be at least partly explained by a considerably lower mean body weight of the patients (64.0 vs. 74.1 kg) in one study [4] and by the use of a larger dialyzer surface area (2.0 vs. 1.7 m^2) and slightly higher blood flow rates (311 vs. 300 ml/min) in the other trial [6]. Therefore and in spite of the methodological shortcomings addressed, the measurement of polyclonal λFLC reduction ratio in plasma could serve as an additional valuable clinical tool to distinguish between different MCO dialyzers, while for monoclonal λFLC, such relevance is less obvious. Depending on the results of further investigations, polyclonal λFLC elimination from plasma may even be suited to elegantly replace the much more complex determination of albumin loss, which is relevant for clinical safety.

Several limitations of the present study need to be addressed. These include the single-center design, non-blinding of the dialyzers, as well as only few efficacy measurements with each filter, but, as the study represents a rather technical approach, the very small sample size may have particularly impacted on the results of the comparative statistical analysis. Furthermore, based on the accredited laboratory's participation in the mandatory round robin tests, λFLC determination was performed with the monoclonal N-Latex and the polyclonal Freelite assays in a practical approach, without further validating the test methods. A new assay based on polyclonal antibodies with ELISA detection (Sebia FLC) has recently been introduced [15]. An additional comparison of the present results also with this test method would have been certainly interesting.

5 | CONCLUSIONS

The new ELISIO expands the choice of dialyzers for MCO hemodialysis and thus more adequate dialysis therapy in order to contribute to the anticipated improvement in patient outcomes. In the present clinical trial, it

achieved removal of an extended range of middle molecules during hemodialysis at a comparable level to the reference Theranova filter, but with less albumin loss. To limit albumin loss to the observed level without compromising or by even enhancing larger middle-molecule elimination, that is, refining the molecular weight retention curve of the dialysis membrane, has been unmatched so far. It represents an outstanding achievement of engineering in which the interplay between the chemical composition of the membrane and the physicochemical factors of membrane spinning technology and sterilization process has been optimized.

Determination of polyclonal free lambda-light chain (λFLC) removal from plasma with the Freelite assay represents a valuable, clinically relevant approach to evaluate efficacy of hemodialysis in end-stage kidney disease patients and particularly to distinguish between different MCO dialyzers. The results for monoclonal λFLC of the N-Latex assay were not conclusive. The two assays cannot be used interchangeably because the resulting plasma concentrations differ considerably.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare. M. R. and H. D. L. are full-time employees of eXcorLab GmbH.

CLINICAL TRIAL REGISTRATION

The study was registered at the German Register for Clinical Trials (DRKS00026806).

PATIENT CONSENT

All patients participating in the study gave written informed consent including approval for publication of the study data.

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